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Original Research

Open-label, multicentre, randomised, phase II study of the EpSSG and the ITCC evaluating the addition of bevacizumab to chemotherapy in childhood and adolescent patients with metastatic soft tissue sarcoma (the BERNIE study)

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Abstract ***Purpose:*** We evaluated the role of bevacizumab as part of the multi-modality treatment of children and adolescents with metastatic rhabdomyosarcoma (RMS) or non-rhabdomyosarcoma soft tissue sarcoma (NRSTS).
Patients and methods: Eligible patients aged ≥6 months to <18 years were randomised to receive induction chemotherapy (four cycles of IVADo + five cycles of IVA, ±bevacizumab), surgery and/or radiotherapy, followed by maintenance chemotherapy (12 cycles of low-dose cyclophosphamide + vinorelbine, ±bevacizumab). The primary objective was event-free survival (EFS) evaluated by an independent radiological review committee.
Results: One hundred and fifty-four patients were randomised to receive chemotherapy alone (n = 80) or with bevacizumab (n = 74). At the data cut-off for the primary efficacy analysis, median EFS was 14.9 months (95% confidence interval [CI]: 10.8–35.9) with chemotherapy and 20.6 months (95% CI: 15.2–24.9) with bevacizumab plus chemotherapy (stratified hazard ratio [HR] = 0.93; 95% CI: 0.61–1.41; $P = 0.72$). The HR for EFS in patients with RMS (n = 103) was 1.24 (95% CI: 0.73–2.09) versus 0.64 (95% CI: 0.32–1.26) for those with NRSTS (n = 49). Objective response rate was 36.0% (95% CI: 25.2–47.9) with chemotherapy and 54.0% (95% CI: 40.9–66.6) with bevacizumab plus chemotherapy (difference of 18.0%; 95% CI: 0.6–35.3). There were no treatment-related deaths and no increased incidence of grade 3/4 toxicities with bevacizumab.
Conclusion: The addition of bevacizumab to chemotherapy appeared tolerable in children and adolescents with metastatic RMS/NRSTS, but the primary end-point of EFS did not show statistically significant improvement.
Trial registration: ClinicalTrials.gov, NCT00643565.
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1. Introduction

Soft tissue sarcomas (STSs) are a heterogeneous group of malignant tumours, in paediatrics conventionally divided into rhabdomyosarcoma (RMS) and non-rhabdomyosarcoma STS (NRSTS), with NRSTS subdivided into multiple histological subtypes [1]. RMS is the most common form of STS in children [2]. Multimodality treatment, including surgery, radiotherapy and chemotherapy, allows 3-year overall survival (OS) in 80–85% of the patients presenting with localised RMS [3,4]. However, the prognosis for patients with metastatic RMS is poor [5–7]. In a pooled analysis of studies in children with metastatic RMS, the 3-year event-free survival (EFS) was only 27% [5]. Furthermore, lack of improvement with conventional chemotherapy has highlighted the need for new and effective treatments [8]. NRSTS are poorly sensitive to chemotherapy; however, multi-modality treatments that include chemotherapy have increasingly been attempted [9,10].

Significant overexpression of the angiogenic factor, vascular endothelial growth factor (VEGF), has been reported in adult STS [11,12]. Anti-VEGF monoclonal antibodies inhibit tumour angiogenesis in preclinical paediatric tumour models, including RMS [13,14]. Bevacizumab, an anti-VEGF monoclonal antibody, is approved for use in a range of adult tumours in combination with chemotherapy, and was well tolerated in a phase I study in children with refractory solid tumours [15]. The present study evaluated the efficacy of the addition of bevacizumab to chemotherapy in childhood and adolescent patients with metastatic STS.

2. Methods

2.1. Study design

This open-label, multicentre, randomised phase II study evaluated the addition of bevacizumab to standard chemotherapy in children and adolescents aged ≥6 months to <18 years with untreated metastatic RMS or NRSTS (BO20924/ITCC-006; ClinicalTrials.gov: NCT00643565).

Full eligibility criteria are described in Supplementary Table S1. Any wounds, tumour-related bleeding or clotting diathesis were to be healed/resolved within the

3 weeks of randomisation. Key exclusion criteria included: prior anti-tumour treatment, central nervous system involvement or spinal cord compression, tumour invading a major blood vessel wall or previous malignant tumours.

The protocol was approved by applicable ethics committees and institutional review boards, and the study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice. Written informed consent was obtained from the parents, patients or legally acceptable representatives before any study-related procedures.

2.2. Treatment

Patients were randomised (1:1) through a central stratified block procedure, with randomisation numbers generated by an interactive voice response system. Patients were stratified by age (≥6 months to <2 years versus ≥2 to <12 years versus ≥12 to <18 years) and disease risk (high-risk metastatic RMS versus non-high-risk metastatic RMS versus NRSTS). High-risk metastatic RMS was defined as at least two of the following: age ≥10 years, unfavourable primary tumour location (i.e. trunk and extremities), bone or bone marrow metastases or metastases in >2 organs [5].

Study treatment spanned 18 months. Induction therapy included 9 × 21-d cycles of chemotherapy, comprising four cycles of IVADo (ifosfamide, vincristine, actinomycin-D, and doxorubicin), followed by five cycles of IVA [16]. Patients were randomised to receive (experimental arm) or not receive (control arm) bevacizumab 7.5 mg/kg every 3 weeks on day 1 of each cycle. Omission of the first two bevacizumab infusions was permitted in cases with a recent history of surgery or biopsy, traumatic injury, bone fracture where the wound or fracture had not satisfactorily healed, tumour-related bleeding or oozing or transient clotting diathesis.

Maintenance chemotherapy comprised 12 × 28-d cycles of low-dose cyclophosphamide and vinorelbine [17], with bevacizumab 5.0 mg/kg every 2 weeks on days 1 and 15 of each cycle in the experimental arm.

2.3. Objectives

The primary objective was to evaluate the efficacy of the addition of bevacizumab to standard chemotherapy in children and adolescents with metastatic RMS and NRSTS, in terms of EFS as assessed by an independent radiological review committee (IRC). Secondary objectives were to determine the safety, tolerability, and efficacy of the addition of bevacizumab to chemotherapy, in terms of: adverse events (AEs); treatment discontinuation, modification or delay; objective response rate (ORR) in patients with measurable disease at baseline, according to Response Evaluation Criteria in Solid Tumors (RECIST) v1.0 every 3 months until the start of local therapy; OS; duration of response (DoR); and the pharmacokinetic profile of bevacizumab (reported separately [18]).

2.4. Assessments

Assessments included: magnetic resonance imaging and/or computed tomography scan of the primary and metastatic sites; bone scintigraphy or fluorodeoxyglucose-positron emission tomography scan; bilateral bone marrow aspiration and trephine biopsies; and cerebrospinal fluid evaluation, as appropriate. AEs were graded using National Cancer Institute Common Terminology Criteria for Adverse Events v3.0.

2.5. Statistical analysis

Assuming a 1-year EFS of 59% in the control arm and 74% in the experimental arm (median EFS of 15.8 and 27.6 months, respectively), corresponding to a hazard ratio (HR) of 0.57 over a 48-month recruitment period and minimum follow-up of 19 months after the last patient was randomised, then 100 events were required to achieve 80% power of the log-rank test (two-sided 5% alpha level). Allowing for a 7% dropout rate, 75 patients per treatment arm were required.

The primary end-point was the duration of EFS, defined as the time between randomisation and disease progression, recurrence (assessed by the IRC), documented evidence of no response after three cycles of induction chemotherapy (derived from IRC response data), second primary cancer or death due to any cause. Data for patients who had not experienced an event by the time of clinical cut-off were censored at the date of the last disease assessment before the clinical cut-off date. Data for patients who did not have any post-baseline disease assessments (e.g. early withdrawals) were censored at the time of randomisation. Kaplan–Meier curves and estimates of median time to event, with corresponding confidence intervals (CIs) were produced. The stratified log-rank test was used to compare EFS between treatment arms at the two-sided 5% alpha level.

IRC-assessed ORR before local therapy was defined as complete or partial response determined on two consecutive occasions ≥4 weeks apart. The difference in ORR between treatment arms was tested in an exploratory manner using a chi-squared test with Schouten correction; 95% Clopper–Pearson CIs were calculated for the ORR and 95% Hauck-Anderson CIs for the difference in ORR. Kaplan–Meier estimates and Brookmeyer–Crowley 95% CIs were produced for DoR. OS was defined as the time between randomisation and death from any cause.

A futility analysis on available safety data was performed after 80 patients had completed six cycles of

induction therapy and ORR had been assessed. The primary analysis of safety and efficacy was performed 19 months after the last patient was randomised.

3. Results

3.1. Patients

Between July 2008 and October 2013, 154 patients were randomised to receive chemotherapy (n = 80) or bevacizumab plus chemotherapy (n = 74; intent-to-treat [ITT] population). The ITT population comprised 103 patients with RMS (high-risk, n = 78) and 49 with NRSTS. Two patients were enrolled where subsequent pathology yielded other diagnoses (one Wilm's tumour, one Ewing's sarcoma). Four randomised patients did not receive study treatment (Supplementary Fig. S1). Baseline characteristics were generally balanced, but there were slightly more males in the experimental arm and more patients with alveolar RMS in the control arm (Supplementary Table S2).

3.2. Efficacy

At the data cut-off point for the primary efficacy analysis (May 31, 2015), the median survival follow-up was 20.5 months in the control arm and 25.0 months in the experimental arm. At this time, 42 patients (52.5%) in the control arm (death, n = 18; tumour progression, n = 18; no response after 3 cycles, n = 3; and tumour recurrence, n = 1) and 51 patients (68.9%) in the experimental arm (death, n = 22; tumour progression, n = 28; and tumour recurrence, n = 1) had experienced an EFS event according to the IRC. Median EFS by IRC (imaging results only) was 14.9 months (95% CI: 10.8–35.9) with chemotherapy versus 20.6 months (95% CI: 15.2–24.9) with bevacizumab plus chemotherapy (stratified HR = 0.93; 95% CI: 0.61–1.41; $P = 0.72$; Fig. 1A). Median EFS by investigators (full clinical information available) was 12.5 months (95% CI: 9.3–18.6) with chemotherapy versus 18.9 months (95% CI: 14.7–25.4) with bevacizumab plus chemotherapy (stratified HR = 0.71; 95% CI: 0.47–1.07; Fig. 1B). The 1-year EFS rate by IRC was 57% (95% CI: 44.6–67.6) with chemotherapy and 75% (95% CI: 63.1–83.8) with bevacizumab plus chemotherapy; 2-year EFS rates were 41% (95% CI: 28.8–52.3) in the control arm and 41% (95% CI: 29.4–53.0) in the experimental arm. The HR for IRC-assessed EFS was 1.24 (95% CI: 0.73–2.09) in patients with RMS and 0.64 (95% CI: 0.32–1.26) in patients with NRSTS.

Six patients in the control arm and one patient in the experimental arm had stable disease. This was confirmed by a central radiological review committee in five cases (all in the control arm), and these contributed to an event of treatment failure in the primary EFS end-point.

Twenty-seven patients in the control arm and 34 patients in the experimental arm had an IRC-confirmed objective response before local therapy. ORR by IRC was 36.0% (95% CI: 25.2–47.9) with chemotherapy and 54.0% (95% CI: 40.9–66.6) with bevacizumab plus chemotherapy (difference: 18.0%; 95% CI: 0.6–35.3) (Supplementary Table S3). Response rates according to histology were also higher in the experimental arm (Supplementary Tables S3 and S4). Median DoR was 17.5 months (95% CI: 12.3–25.2) in the experimental arm and was not reached in the control arm.

OS data will be presented once they are mature.

3.3. Biomarker analysis

At baseline, 77 patients (48 control arm, 29 experimental arm) had placental growth factor (PlGF) serum/plasma measurements, and 52 patients (29 control arm, 23 experimental arm) had tumour VEGF-A (tVEGFA) measurements. Baseline demographic characteristics were balanced between the treatment arms. EFS and OS analyses in the biomarker-evaluable population showed comparable results to the ITT population; no predictive value could be concluded for these biomarkers (data not shown).

3.4. Treatment exposure

The median number of bevacizumab dose administrations was 19.0 (range 6–27). During the induction phase, 17 patients (23.9%) did not receive the first bevacizumab dose due to protocol-specified conditions requiring it to be omitted. When starting maintenance treatment, 51 patients (71.8%) did not receive the first bevacizumab dose as they were still receiving radiotherapy or waiting for the protocol-specified 4-week period between radiotherapy and bevacizumab to elapse.

Exposure to the components of induction chemotherapy was comparable between the treatment arms, but exposure to maintenance chemotherapy was slightly higher in the experimental arm (Supplementary Table S5); most patients received ≥90% of the planned dose, with the exception of maintenance vinorelbine and cyclophosphamide.

3.5. Safety

No AE leading to death was reported. There was no increase in the incidence of grade 3/4 AEs with the addition of bevacizumab (Table 1). The rate of grade 3/4 AEs of special interest was comparable between the treatment arms (12.7% in each; Table 1). Grade 3/4 chemotherapy-related AEs were reported in 89.9% of the patients receiving chemotherapy and 94.4% of the patients receiving bevacizumab plus chemotherapy and were mostly haematological (86.1%

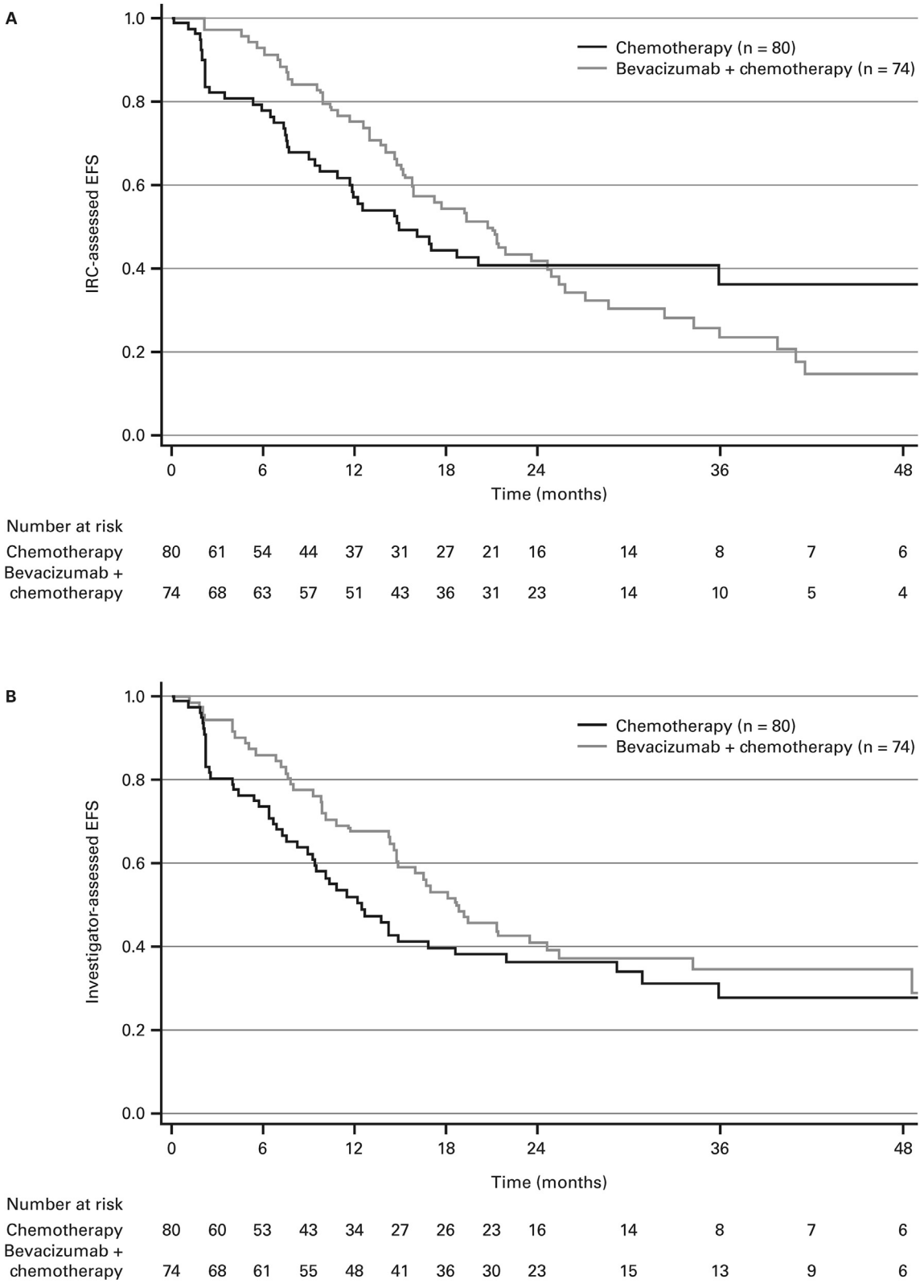

Fig. 1. Kaplan–Meier plots of EFS in the ITT population: IRC assessed (primary end-point) (A); investigator assessed (B). EFS, event-free survival; IRC, independent radiological review committee; ITT, intent-to-treat.

and 93.0% of patients, respectively; Table 1). Two patients (2.5%) in the control arm and three patients (4.2%) in the experimental arm experienced grade 3/4 cardiac events.

AEs leading to chemotherapy discontinuation were reported in six patients in each of the control (7.6%) and experimental (8.5%) arms. AEs leading to bevacizumab discontinuation occurred in eight patients (11.3%), with

Table 1
Overview of AEs in the safety population.

Patients, n (%)	Chemotherapy (n = 79)	Bevacizumab + chemotherapy (n = 71)
Median duration of safety observation,[a] months	9.3	18.5
Any AE	79 (100)	71 (100)
Any treatment-related AE	77 (97.5)	71 (100)
Any serious AE	68 (86.1)	66 (93)
Any treatment-related serious AE	63 (79.7)	63 (88.7)
Grade 3/4 AE	79 (100)	70 (98.6)
Grade 3/4 chemotherapy-related toxicity	71 (89.9)	67 (94.4)
Haematological	68 (86.1)	66 (93)
Neurological	11 (13.9)	7 (9.9)
Renal	6 (7.6)	1 (1.4)
Cardiac	2 (2.5)	3 (4.2)
Grade 3/4 AEs with a difference of ≥5% between treatment groups		
Febrile neutropenia/febrile bone marrow aplasia	62 (78.5)	60 (84.5)
Neutropenia	52 (65.8)	54 (76.1)
Anaemia	43 (54.4)	49 (69.0)
Thrombocytopaenia	31 (39.2)	24 (33.8)
Decreased appetite	12 (15.2)	15 (21.1)
Hypokalaemia	11 (13.9)	5 (7)
Hypophosphataemia	4 (5.1)	0
Mucosal inflammation	13 (16.5)	18 (25.4)
Stomatitis	10 (12.7)	5 (7)
Constipation	0	4 (5.6)
Device-related infection	7 (8.9)	1 (1.4)
Alanine aminotransferase increased	0	4 (5.6)
Grade 3/4 AE of special interest	10 (12.7)	9 (12.7)
Bleeding/haemorrhage	6 (7.6)	2 (2.8)
Arterial thromboembolic events	3 (3.8)	1 (1.4)
Congestive heart failure	0	2 (2.8)
Wound-healing complication	0	2 (2.8)
GI perforation	0	2 (2.8)
Venous thromboembolic events	1 (1.3)	0
Hypertension	0	0
Proteinuria	0	0
Fistula/abscess	0	0
Posterior reversible encephalopathy syndrome	0	0
AE leading to death	0	0
Discontinued bevacizumab due to AE	0	8 (11.3)
Discontinued any study treatment due to AE	6 (7.6)	11 (15.5)

AE = adverse event; GI = gastrointestinal.
[a] From administration of first dose of study treatment to 28 d after last dose of study treatment.

four of these patients experiencing cardiac events (one case each of grade 1, 2 and 3 left ventricular dysfunction and one case of grade 3 cardiac failure). There were no cardiac events leading to treatment discontinuation in the control arm. Other AEs leading to bevacizumab withdrawal were febrile neutropenia, urinary tract infection, vocal cord paresis, renal impairment and renal microangiopathy (one patient each).

Six patients (7.6%) in the control arm and 11 patients (15.5%) in the experimental arm discontinued at least one component of study treatment due to treatment-related toxicity (Table 1).

More patients in the experimental arm (88.7%) than in the control arm (67.1%) experienced AEs leading to dose delay/interruption of either chemotherapy or bevacizumab. Overall, 59.2% of the patients in the experimental arm experienced AEs leading to dose delay/interruption of bevacizumab, the most common event being neutropenia (n = 18; 25.4%).

4. Discussion

This randomised study did not meet its primary end-point of improved EFS with bevacizumab plus chemotherapy in children and adolescents with metastatic RMS and NRSTS. Bevacizumab in combination with chemotherapy in relapsed RMS did not improve EFS compared with historical controls in a North American study [19]. The observed 1-year EFS (57% control arm, 75% experimental arm) and 2-year EFS (41% in both arms) rates are comparable with published data [5,8], despite the fact that 51% of the patients had high-risk metastatic RMS.

By IRC, a higher response rate of 54.0% (95% CI: 40.9–66.6) was seen in the experimental arm compared with 36.0% (95% CI: 25.2–47.9) in the control arm. This is consistent with findings for other anti-angiogenic agents in STS [20–22], but correlation between ORR and OS is controversial in STS [9,23].

The safety profile of bevacizumab was consistent with its known safety profile in adults. More discontinuations due to cardiac events occurred in the experimental arm than in the control arm (4 versus 0, respectively), possibly due to the investigators' concern about potential bevacizumab-related cardiotoxicity.

No prognostic value could be concluded for baseline PlGF or tVEGFA as biomarkers for the efficacy of bevacizumab treatment.

The management and conduct of the study, involving collaboration between academia and industry, and investigation of an innovative drug within a complex paediatric front-line therapy protocol, are important strengths of this study. The design was based on clinical trials in adults with the additional limitation of the slower recruitment in this rare population. The assumptions were very optimistic. The lack of statistical significance for the primary end-point of IRC EFS may reflect the fact that the sample size, although realistic for this rare population, was inadequate to detect a treatment effect and included patients with disparate tumour types of different predicted chemosensitivities. The study was not designed to show

benefit in tumour subtypes, but HRs suggested no improvement in IRC EFS in RMS, the largest subtype. NRSTS subgroups were too small to draw conclusions. The apparent difference in EFS by IRC and investigators may be explained by investigators having access to clinical information as well as the knowledge of the imaging on which the IRC judgements were based.

In summary, the addition of bevacizumab to the chemotherapy backbone appeared tolerable in children and adolescents with metastatic RMS or NRSTS, but the primary end-point of EFS did not show statistically significant improvement. Currently, these data suggest no role for bevacizumab in metastatic RMS, but further investigation in specific NRSTS subtypes might be considered.

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Conflict of interest statement

JCC has acted in a consulting/advisory role for F. Hoffmann-La Roche Ltd and Merck and received travel, accommodation or expenses from Roche; JHMM has acted in a consulting/advisory role for F. Hoffmann-La Roche Ltd and received travel, accommodation or expenses from Roche; MC has acted in a consulting/advisory role for F. Hoffmann-La Roche Ltd; GB has acted in a consulting/advisory role for Loxo Oncology and received research funding from IndenaSpA, and travel, accommodation or expenses from Merck; DO has received travel, accommodation or expenses from Chugai Pharma; KM has received honoraria from Bayer UK and acted in a consulting/advisory role for Bayer; RRR has acted in a consulting/advisory role for Roche and received royalties from Springer and Thieme; MH is employed by F. Hoffmann-La Roche Ltd, owns stock in Roche and has patent or intellectual property interest in Roche; JB is employed by F. Hoffmann-La Roche Ltd; SF-R is employed by F. Hoffmann-La Roche Ltd, owns stock in Roche and has received travel, accommodation or expenses from Roche. All remaining authors have declared no conflicts of interest.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.ejca.2017.06.015.

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